Decree of the Rector n. 1155 of 10/11/2023
Competition for awarding 1 research grant at the University of Udine

DISCLAIMER:
The official and legally binding call for applications is in Italian only.
This document cannot be used for legal purposes and is only meant to provide information in English on the call for applications (Decree of the Rector n. 1155 of 10/11/2023). Please refer to the official call published on: https://www.uniud.it/it/albo-ufficiale

Any change and integration will be made available on the above mentioned web page. Therefore, no personal written communication regarding the examination date and/or competition results shall be provided to applicants.

Annex 1

Competition announcement for the assignment of 1 research grant at the University of Udine, entitled "Design of an in vitro model for studying the role of Malin in the development of Lafora syndrome" SSD: MED/03 (principal investigator, Giuseppe Damante)

Art. 1

A selection procedure is hereby launched for the award of 1 research grant at the University of Udine, as identified in Attachment A which constitutes an integral part of the present announcement.
The research grant is linked to the research project and is subject and conditioned upon the relative funding.
The fellowship may be renewed, in compliance with Art. 22, Law No. 240 of 30 December 2010 (as in the text in force before the implementation of the Conversion Law of the D.L. 36/2022, L. 79/2022), Law No. 11 of 27 February 2015, and the current regulations of the University of Udine for awarding research grants, issued with the Rector's Decree No. 182 of 31 March 2021. The renewal is subject to the scientific coordinator's positive assessment of the researcher's activities, an adequate scientific rationale, and a corresponding financial covering.

The research fellowship does not give rise to any right with regards to accessing University posts.

Any personal communication to candidates related to this selection will be sent exclusively to the email address indicated when registering for the selection, as mentioned in Art. 5.

Art. 2

The research grant described in this competition announcement and the required qualifications to apply for the position are identified in Attachment A. The lack of the admission requirements leads to the automatic exclusion from the competition procedure.

Possession of a PhD or equivalent degree obtained abroad or, only for the interested areas, of a medical specialization accompanied by an adequate scientific production, constitutes a preferential qualification for awarding the research fellowship of this selection, if it has not been provided as a mandatory requirement.

Candidates in possession of a specialization qualification in the medical area obtained abroad must also attach the recognition decrees issued by the Italian Ministry of Health in order to avail themselves

of the qualification of specialist doctor and of the title of surgeon. These recognition decrees are also required if the qualification has already been recognized in another country of the European Union. http://www.salute.gov.it/ProfessioniSanitariePubblico/

For the only purpose of the admission to the competition, the Examining Board (Art. 7) shall assess the equivalence of the qualification obtained abroad, except for the evaluation of the medical specialization qualification to which Article 38 of the Legislative Decree 165/2001 and subsequent modifications and additions, and EU regulations on the matter, shall be applied.

The Examining Board will proceed to the evaluation of the qualification obtained abroad according to the documentation attached to the application form. The Examining Board may exclude the candidate if the submitted documentation does not provide sufficient information for the assessment.
Therefore, applicants must enclose all the documentation in their possession relating to their qualification in order to provide the Examining Board with sufficient information for assessment.

Candidates holding a qualification issued by a **European Research Area country**, if successful, must submit, if not already attached to the application form one of the following options:

- Supplement Diploma in English issued by the competent University.
- CIMEA Certificate of comparability of the foreign qualification, issued by CIMEA (Information Centre on Academic Mobility and Equivalence) via the "diplo*me*" service at https://cimea.diplome.eu/udine/#/auth/login

Candidates holding a qualification issued by a **non-European Research Area country**, if successful, must submit, if not already attached to the application form one of the following options:

- Declaration of the on-site value of the qualification and the certificate relating to the degree with examinations and grades. A certificate in a language other than Italian or English must be accompanied by an official translation into one of these languages (certified by the competent diplomatic-consular authority or certified by a court in Italy).
- CIMEA Certificate of comparability of the foreign qualification, issued by CIMEA (Information Centre on Academic Mobility and Equivalence) via the "diplo*me*" service at https://cimea.diplome.eu/udine/#/auth/login

If the Supplement Diploma or the statement/attestation of comparability are not available when signing the contract, the applicant must demonstrate that he/she has requested the documentation and submit it as soon as possible.

Any exclusion from the selection procedure due to lack of eligibility requirements, absence of required documents, failure to sign the selection application or submission of the selection application in a manner different from what is provided for in this call for applications will be communicated to applicants exclusively at the email address indicated in the application form.

Art. 3

The research grant referred to in this call for applications cannot be awarded:

a. to employees of Universities and the entities referred to in Article 22, section 1, of Italian Law no. 240 of 30 December 2010 (in the text prior to the reform introduced by Law no. 79 of 29 June 2022);
b. to those who have already been awarded research grants pursuant to Italian Law no. 240 of 30 December 2010 (prior to the reform introduced by Law no. 79 of 29 June 2022) for the maximum period provided by law, even if not continuously, excluding the period in which the grant was used in conjunction with the doctorate, up to the legal term of the relative course;

c. to those who have already benefited from research grants and fixed-term researcher contracts provided for, respectively, in Articles 22 and 24 of Italian Law no. 240 of 30 December 2010 (in the text prior to the reform introduced by Law no. 79 of 29 June 2022), for a total of 12 years, even if not consecutive;
d. to anyone who has a degree of kinship or affinity, up to and including the fourth degree, with:
   - the Rector, the Director General or a member of the Board of Directors of the University of Udine;
   - the scientific supervisor or a professor/researcher belonging to the department or organisation hosting the research grant in question.

The research grant provided for in this call for applications cannot be combined:

a) with scholarships of any kind, except for those granted by Italian or foreign institutions to supplement, by means of stays abroad, the fellow's training or research activities;
b) with other research grants;
c) with an employment relationship, even if part-time, without prejudice to the relevant provisions for employees of public administrations.

The grant awarded under this call for applications is also incompatible with simultaneous attendance at university degree courses, either Bachelor's degree or Master's degree courses, research Doctorates with scholarships and medical specializations, in Italy or abroad.

Art. 4

Applicants must enclose with their application, under penalty of exclusion, the following documents:

a) their professional scientific CV, highlighting the candidate's aptitude for carrying out and implementing the research project (Attachment A);
b) their identity card, their passport or any other identification document[1];
c) (for candidates with a foreign qualification only) certification or self-certification of both the academic qualification required for the admission to the selection, and of the exams (with evaluation) took during the period of study abroad, and of any other document that can be useful to the evaluation of the degree by the Examining Board.

Applicants can attach to the application, publications and any other certification considered useful to demonstrate the qualification based on the research program (Attachment A) and to certify any research activity accomplished at public or private institutes (indicating the starting and ending date and the duration).

The documents and qualifications mentioned above must be submitted in Italian or English. Those that are not as requested will not be evaluated. Documents originally written in a language other than Italian or English must come with a translation in Italian or English, that the candidate will do on its own responsibility. The translation can be an abstract concerning the thesis.

Italian and Community candidates wishing to submit qualifications referring to conditions and facts attested by Public Administrations must proceed exclusively with self-certification.
Non-EU citizens legally residing in Italy may self-certify only data that can be verified or certified by Italian public bodies. They may also use declarations in lieu when provided for by an international convention between Italy and the declarant's country of origin.
Non-EU citizens not residing in Italy cannot self-certify.

Only the qualifications possessed by the candidate on the date the application form is submitted and submitted in accordance with the procedures set out in Article 5 will be assessed.

[1] Please be aware that the residence permit is not an identification document.

Failure to submit mandatory documents provided for in this article will constitute grounds for exclusion from the selection.

Art. 5

The submission of the applications for the present call starts on November 16, 2023 at 2:00 pm (Italian time) and ends on December 7, 2023 at 2:00 pm (Italian time).

The application to take part in the selection must be completed, under penalty of exclusion, using the appropriate online procedure, available at the link https://pica.cineca.it/
The procedure involves an applicant registration step, for those who do not already have an account, and then an application completion step.

Once completed, the online application must be signed in the manner described in the online procedure (manual signature with attached identity document or digital signature), under penalty of exclusion from selection. The application does not have to be signed if you access the above-mentioned online procedure using your SPID ID.

The qualifications referred to in Article 4 must be attached to the application in .pdf format. Individual .pdf files may not exceed 30MB.

The application for participation in the selection is automatically sent to the University of Udine with the definitive closing of the online procedure.

The University Administration:
- is not responsible if it is impossible to read the submitted documentation in electronic format due to damaged files;
- shall not accept or take into consideration qualifications or documents received in paper form or by any means other than what is specified in this article.

Reference to documents or publications already submitted in connection with other competitions is not allowed.

The Administration is not responsible for any missing document or communication because of inaccurate indication of residence and/or address submitted by the candidate during the application. Also, the Administration is not responsible if the candidate has not communicated changes in this information, or has communicated them too late. The Administration is also not responsible for any postal or telegraphic problems not attributable to the Administration itself.

Applicants are advised not to wait until the last few days before the closing date to submit their application. The University accepts no responsibility for any malfunctions due to technical problems and/or overloading of the communication line and/or application systems.

Art. 6

The selection procedure is held in accordance with the modality indicated in Attachment A.

The test will aim to assess the general preparation, experience and aptitude for research of the candidate. It will consist in the evaluation of the professional scientific curriculum, of the publications and qualifications presented, and of the interview, where foreseen.

Art. 7

The Examining board for the competition is identified in Attachment A of the present competition announcement, of which it is an integral part.

At its first meeting, the Examining board shall appoint its President and Secretary, and establish the criteria and methods for evaluating the qualifications and the interview, where foreseen.

The results of the qualifications assessment must be disclosed to applicants during the interview, where foreseen.

The Examining board can award a maximum of 100 points (one hundred out of one hundred) to the selection.

At the end of the evaluation procedure, the Examining board shall formulate the general merit list based on the overall score of each candidate, and draw up the minutes of the whole competition procedure.

Based on the ranking list, the assignment is awarded to candidates who have obtained a minimum overall score of 70/100 (seventy out of one hundred).

The Examining board's judgement is final.

The ranking list will be made public exclusively through publication on the University's official website.

Applicants will not be notified of the outcome of the evaluation.

Those who do not declare their acceptance of the research grant and do not present themselves at the research centre within the deadline communicated by the latter, even if not formally, shall lose the right to receive it. Exceptions to this term will only be granted in cases of documented force majeure.

Before signature of the research grant contract, the candidate awarded of reference research grant must submit a copy of the vaccination booklet or related certificate, and intradermal reaction – sec. Mantoux (performed in the last 12 months). The selected candidate will have to undergo any health assessment deemed necessary by the competent doctor and aimed at issuing the assessment of suitability for the specific task according to the protocol of the host structure. The signature of the contract will be possible only after obtaining the judgment of suitability for the specific task by Azienda Sanitaria Universitaria Friuli Centrale (ASU FC).

Art. 8

The research activity cannot be started before signing the contract defining the terms and conditions of the collaboration.

The activity covered by the research grant must have the following characteristics:

a) it must be carried out as part of the research programme covered by the grant and not be a merely technical support to it;
b) it must have a close connection with the realization of the research program for which the winner of the grant has been awarded the contract;
c) it must be continuous and, in any case, temporally defined, not merely occasional, and in coordination with the overall activity of the University;
d) it must be carried out autonomously, solely within the limits of the programme prepared by the programme supervisor, without predetermined working hours.

The researcher is required to submit a detailed written report on the work carried out and the results achieved, accompanied by the opinion of the scientific supervisor, to the reference organisation at the intervals set out in the contract. The researcher must also submit interim reports and timesheets, if requested by the reference organisation.

Either the fellow or the reference organisation may withdraw from the contract.
The reference organisation may terminate the contract not only in the cases referred to in Article 9, sections 2 and 3, of the "Internal rules for awarding research grants pursuant to law 240 of 30 December 2010" of the University of Udine, but also in the event the research project and therefore the financial coverage on which the research grant is based cease to exist.

With regard to accident insurance and third-party liability, the provisions of art. 3 c. 5 of the "Internal rules for awarding research grants pursuant to Italian Law no. 240 of 30 December 2010" of the University of Udine, issued by Rector's Decree no. 182 of 31 March 2021, are applied.
The Azienda Sanitaria Universitaria Friuli Centrale (ASU FC), by authorizing with a subsequent deed the access of the selected candidate to its facilities, ensures insurance cover for professional risks and third-party liability in the course of the authorized activity. The insurance policy for accidents and occupational diseases remains at the expense of the selected candidate. In the absence of such policy, the selected candidate will not be allowed to access the facilities of the Azienda Sanitaria Universitaria Friuli Centrale (ASU FC), and it will not be possible to proceed with the signature of the contract.

Art. 9

The following legal dispositions shall apply to the grant referred to in this call for applications:
- for tax matters, the provisions of Article 4 of Italian Law no. 476 of 13 August 1984, as subsequently amended and supplemented;
- for social security matters, the provisions of Article 2(26) *et seq*. of Italian Law no. 335 of 8 August 1995, as subsequently amended and supplemented;
- for mandatory maternity leave, the provisions of the Italian Ministerial Decree of 12 July 2007;
- with regard to sick leave, the provisions of Article 1(788) of Italian Law no. 296 of 27 December 2006 and subsequent amendments.

During the period of mandatory maternity leave, the allowance paid by INPS according to Art. 5 of the Italian Ministerial Decree of 12 July 2007 is supplemented by the University up to the full amount of the research grant.

The grant will be paid in monthly instalments.

Art. 10

The data collected as part of the procedure referred to in Art. 5 are necessary to properly manage the selection procedure, for any subsequent management of the research grant and for purposes related to managing services provided by the University. The University of Udine is the Data Controller. At any time, the data subject may request access, rectification and, depending on the University's institutional purposes, cancellation and restriction of processing or oppose the processing of their data. The data subject can always lodge a complaint with the Italian Data Protection Authority. The complete disclosure is available on the University of Udine website in the "Privacy" section, accessible from the home page www.uniud.it Direct Link: https://www.uniud.it/it/it/pagine-speciali/guida/privacy

Art. 11

For all matters not expressly mentioned in this call for applications, refer to the regulations in force on the subject cited in the introduction and to the "Internal rules for awarding research grants pursuant to Italian Law no. 240 of 30 December 2010" of the University of Udine, issued by Rector's Decree no. 182 of 31 March 2021.

Art. 12

The procedure supervisor is Dr Sandra Salvador, Head of the Research Services Area of the University of Udine.

The Responsible office at the University of Udine is “Area Servizi per la Ricerca - Ufficio Formazione per la Ricerca”, via Mantica n. 31 - 33100 Udine, Italia.

To request information about the call for applications, please complete the following form available on the University of Udine website:
https://helpdesk.uniud.it/SubmitSR.jsp?type=req&accountId=universityofudine&populateSR_id=42105

Attachment A

Responsabile scientifico della ricerca / Principal investigator:

Nome e cognome / Name and surname: Giuseppe Damante
Qualifica / Position: Professore Ordinario / Full Professor
Dipartimento / Department: Area Medica (DAME) / Medicine
Area MUR / Research field: 06 - Scienze Mediche / Medical Sciences
Settore concorsuale e Settore scientifico disciplinare / Scientific sector: 06/A1; MED/03 - Genetica medica

Titolo dell'assegno di ricerca / Topic of the research fellowship "assegno di ricerca":
I bandi sono consultabili dal sito dell'Ateneo, del MUR e di Euraxess / The calls are available on the University, MUR and Euraxess websites

Testo in italiano:

Progettazione di un modello in vitro per lo studio del ruolo della proteina Malina nello sviluppo della Sindrome di Lafora.

Text in English:

Design of an in vitro model for studying the role of Malin in the development of Lafora syndrome.

Obiettivi previsti e risultati attesi del programma di ricerca in cui si colloca l'attività dell'assegnista di ricerca / Foreseen objectives and results of the research programme performed by the research fellow "assegnista di ricerca":
I bandi sono consultabili dal sito dell'Ateneo, del MUR e di Euraxess / The calls are available on the University, MUR and Euraxess websites

Testo in italiano:

Abstract del progetto	La malattia di Lafora (LD) è una rara forma fatale di epilessia mioclonica progressiva, che segue un modello di ereditarietà autosomica recessiva (Pondrelli *et al.* 2021). Alterazioni in *EPM2A* (6q24) o *NHLRC1* (6p22.3) causano la LD (Minassian *et al.* 1998). Esse codificano rispettivamente per la glicogeno fosfatasi laforina e la E3 ligasi malina, entrambe coinvolte nel metabolismo del glicogeno. Il sistema dell'ubiquitina ha un impatto sulla maggior parte dei processi cellulari ed è alterato in numerose malattie neurodegenerative. Tuttavia, si sa poco del suo ruolo nelle malattie neurodegenerative dovute a disturbi del metabolismo del glicogeno, come la malattia di Lafora (LD) (Mitra *et al.* 2022). La LD è infatti caratterizzata dalla presenza di inclusioni intracellulari di glicogeno non sufficientemente ramificato e a catena lunga (poliglucano), note come corpi di Lafora (LB), negli astrociti, nei periciti e nei dendriti neuronali (Gentry *et al.* 2005). Le manifestazioni cliniche sono dovute principalmente all'accumulo patologico di poliglucano da parte dei neuroni, che determina neuroinfiammazione, neurodegenerazione ed epilessia (Burgos et al. 2020).
Obiettivi del progetto	Pertanto, l'obiettivo di questo studio è creare un modello in vitro di malattia di Lafora che presenti l'inattivazione biallelica del gene *NHLRC1*, in modo tale da poter valutare il ruolo della proteina Malina nello sviluppo della patologia.

Stato dell'arte	La malattia di Lafora (LD) è una rara forma fatale di epilessia mioclonica progressiva, che segue un modello di ereditarietà autosomica recessiva. Nella LD si forma glicogeno a catena lunga e meno ramificato, che precipita in corpi poliglucosani (LB) insolubili, che probabilmente determinano la neurodegenerazione e l'epilessia, ossia i sintomi principali della patologia. In genere, la LD esordisce in adolescenti altrimenti sani con mioclonie, crisi visive e convulsive, che nel tempo diventano frequenti e intrattabili. Ciò si associa a un declino comportamentale e cognitivo; alla fine il paziente raggiunge uno stato vegetativo e muore entro 10 anni dall'esordio. I meccanismi molecolari alla base della LD non sono del tutto noti. Tuttavia, recenti ricerche hanno rivelato il coinvolgimento di proteine implicate nel metabolismo del glicogeno, ovvero la glicogeno fosfatasi laforina e il suo partner proteico interagente, l'ubiquitina E3 ligasi malina. Il ruolo del complesso malina-laforina nella regolazione della struttura del glicogeno rimane ancora pieno di incognite.
Descrizione del progetto	L'attività sarà effettuata utilizzando modelli sperimentali *in vitro*. Il progetto si articolerà nelle seguenti fasi: 1. Progettazione e design di gRNA in grado di inserire una mutazione frameshift in omozigosi nel modello cellulare scelto. *Almeno quattro gRNA diverse verranno disegnate sulla regione codificante del gene NHLRC1 tramite appositi tool online.* 2. Esperimenti di gene editing basati sull'utilizzo della gRNA sopracitata e della proteina SpCas9 per l'ottenimento del modello di malattia. *La gRNA verrà clonata all'interno di un plasmide contenente la sequenza codificante della proteina Cas9 e il gene di resistenza alla puromicina. Cellule umane immortalizzate derivanti dal neuroectoderma verranno trasfettate con il costrutto. A 48 ore dal trattamento le cellule verranno trattate e selezionate con puromicina.* 3. Selezione del clone che presenta l'editing desiderato ed espansione dellostesso. *A 72 ore dalla selezione, le cellule verranno piastrate con diluizione limite per garantire la formazione di cloni. Alla fine del procedimento, il DNA verrà estratto e analizzato mediante sequenziamento Sanger e ddPCR.* 4. Valutazione degli effetti della mutazione sulla funzionalità della proteina. *Gli effetti della mutazione verranno analizzati tramite analisi dell'espressione genica (RNA-seq), del legame della proteina ai suoi target (IP e western blotting) e colorazione PAS per la valutazione della produzione di depositi di poliglucano.*
Possibili potenzialità applicative	L'obiettivo finale di questo progetto è quello di identificare il meccanismo patogenetico associato a Malina nella sindrome di Lafora. I risultati attesi avranno un grande impatto sulla comunità scientifica per almeno due motivi. In primo luogo, la creazione di un modello in vitro di malattia permetterà di colmare le lacune sul coinvolgimento del complesso laforina-malina nella genesi e nella progressione di questa devastante

	patologia. In secondo luogo, i dati raccolti in questo progetto permetteranno di identificare Malina come possibile bersaglio terapeutico per una patologia che, ad oggi, non ha terapia.
Bibliografia	Burgos DF, Cussó L, Sánchez-Elexpuru G, Calle D, Perpinyà MB, Desco M, Serratosa JM & Sánchez MP 2020 Structural and Functional Brain Abnormalities in Mouse Models of Lafora Disease. *International Journal of Molecular Sciences* **21** 7771. (doi:10.3390/ijms21207771). Gentry MS, Worby CA & Dixon JE 2005 Insights into Lafora disease: Malin is an E3 ubiquitin ligase that ubiquitinates and promotes the degradation of laforin. *Proceedings of the National Academy of Sciences* **102** 8501–8506. (doi:10.1073/pnas.0503285102). Minassian BA, Lee JR, Herbrick J-A, Huizenga J, Soder S, Mungall AJ, DunhamI, Gardner R, Fong CG, Carpenter S *et al.* 1998 Mutations in a gene encoding a novel protein tyrosine phosphatase cause progressive myoclonus epilepsy. *Nature Genetics* **20** 171–174. (doi:10.1038/2470). Mitra S, Gumusgoz E & Minassian BA 2022 Lafora Disease: current biology and therapeutic approaches. *Revue Neurologique* **178** 315–325. (doi:10.1016/j.neurol.2021.06.006). Pondrelli F, Muccioli L, Licchetta L, Mostacci B, Zenesini C, Tinuper P, Vignatelli L & Bisulli F 2021 Natural history of Lafora disease: a prognostic systematic review and individual participant data meta-analysis. *Orphanet Journal of Rare Diseases* **16** 362. (doi:10.1186/s13023-021-01989-w).

Text in English:

Abstract	Lafora disease (LD) is a rare fatal form of progressivemyoclonic epilepsy that follows an autosomal recessive inheritance pattern (Pondrelli et al. 2021). Alterations in *EPM2A* (6q24) or *NHLRC1* (6p22.3) cause LD (Minassian et al. 1998). They encode for glycogen phosphatase laforin and E3 ligase malin, respectively, both of which are involved in glycogen metabolism. The ubiquitin system impacts most cellular processes and is altered in several neurodegenerative diseases. However, little is known about its role in neurodegenerative diseases due to disorders of glycogen metabolism, such as Laforadisease (LD) (Mitra et al. 2022). LD is indeed characterized by the presence of intracellular inclusions of insufficiently branched, long-chain glycogen (polyglucan), known as Lafora bodies (LB), in astrocytes, pericytes, and neuronal dendrites (Gentry et al. 2005). Clinical manifestations are mainly due to pathological accumulation of polyglucan by neurons, resulting in neuroinflammation, neurodegeneration, and epilepsy (Burgos et al. 2020).
Objectives of the project	Therefore, the aim of this study is to create an in vitro model of Lafora disease that exhibits biallelic inactivation of the *NHLRC1* gene, so that the role of the Malin protein in the development of the disease can be assessed.
State of the art	Lafora disease (LD) is a rare fatal form of progressivemyoclonic epilepsy that follows an autosomal recessive inheritance pattern. In LD, long-chain, less-branched glycogen is formed and precipitates into insoluble polyglucosan (LB) bodies, which likely result in neurodegeneration and epilepsy, i.e., the main symptoms of the disease. Typically, LD typically begins in otherwise healthy adolescents with myoclonus, visual and seizures, which over time become frequent and

	intractable. This is associated with behavioral and cognitive decline; eventually the patient reaches a vegetative state and dies within 10 years of onset. The molecular mechanisms underlying LD are notfully known. However, recent research has revealed the involvement of proteins involved in glycogen metabolism, namely glycogen phosphatase laforin and its interacting protein partner, ubiquitin E3 ligase malin. The role of the malin-laforin complex in regulating glycogen structure remains with full of gaps.
Project description	The activity will be carried out using in vitro experimental models. The project will consist of the following phases: 1. Design of gRNAs capable of inserting a homozygous frameshift mutation into the chosen cell model. *At least four different gRNAs will be designed on the coding region of the NHLRC1 gene using appropriate online tools.* 2. Gene editing experiments based on the use of the above-mentioned gRNA and SpCas9 protein to obtain the disease model. *The gRNA will be cloned within a plasmid containing the coding sequence of the Cas9 protein and the puromycin resistance gene. Immortalized human cells derived from neuroectoderm will be transfected with the construct. 48 hours after treatment, cells will be treated and selected with puromycin.* 3. Selection of the clone that has the desired editing and its expansion. *72 hours after selection, cells will be seeded with limiting dilution to ensure clone formation. At the end of the procedure, DNA will be extracted and analyzedby Sanger sequencing and ddPCR.* 4. Evaluation of mutation effects on protein functions. *The effects of the mutation will be analyzed by gene expression analysis (RNA-seq), binding of the protein to its targets (IP and western blotting), and PAS staining for evaluation of polyglucan deposit production.*
Possible application potentialities	The ultimate goal of this project is to identify thepathogenic mechanism associated with Malin in Lafora syndrome. The expected results will have a great impact on the scientific community for at least two reasons. First, the creation of an in vitro model of the disease will fill in the gaps on the involvement of the laforin-malin complex in the genesis and progression of this devastating disease. Second, the data collected in this project will allow Malin to be identified as a possible therapeutic target for a disease that, to date, has no therapy.
References	Burgos DF, Cussó L, Sánchez-Elexpuru G, Calle D, Perpinyà MB, Desco M, Serratosa JM & Sánchez MP 2020 Structural and Functional Brain Abnormalities in Mouse Models of Lafora Disease. *International Journal of Molecular Sciences* **21** 7771. (doi:10.3390/ijms21207771). Gentry MS, Worby CA & Dixon JE 2005 Insights into Lafora disease: Malin is an E3 ubiquitin ligase that ubiquitinates and promotes the degradation of laforin. *Proceedings of the National Academy of Sciences* **102** 8501–8506. (doi:10.1073/pnas.0503285102). Minassian BA, Lee JR, Herbrick J-A, Huizenga J, Soder S, Mungall AJ,

	Dunham I, Gardner R, Fong CG, Carpenter S *et al.* 1998 Mutations in a gene encoding a novel protein tyrosine phosphatase cause progressive myoclonus epilepsy. *Nature Genetics* **20** 171–174. (doi:10.1038/2470). Mitra S, Gumusgoz E & Minassian BA 2022 Lafora Disease: current biology and therapeutic approaches. *Revue Neurologique* **178** 315–325. (doi:10.1016/j.neurol.2021.06.006). Pondrelli F, Muccioli L, Licchetta L, Mostacci B, Zenesini C, Tinuper P, VignatelliL & Bisulli F 2021 Natural history of Lafora disease: a prognostic systematic review and individual participant data meta-analysis. *Orphanet Journal of Rare Diseases* **16** 362. (doi:10.1186/s13023-021-01989-w).

Struttura dell'Università di Udine presso la quale verrà sviluppata l'attività di ricerca / Department or other structure of the University of Udine where research activities will be carried out:

Dipartimento di Area Medica (DAME) / Department of Medicine

Struttura ospedaliera coinvolta / Hospital facility involved:

Azienda Sanitaria Universitaria Friuli Centrale (ASU FC) SOC Istituto di Genetica Medica

Tipologia di attività assistenziale prevista in relazione alle esigenze del programma di ricerca / Type of care activity scheduled in relation to the needs of the research program:

Nessun contatto con pazienti ma solo con dati clinici sensibili. / No contact with patients but only with sensitive clinical data.

Importo dell'assegno di ricerca (al lordo oneri carico assegnista) / Total grant gross for the research fellowship:

€ 19.367,00

Durata dell'assegno di ricerca / Duration of the research fellowship "assegno di ricerca":

12 mesi / months

Finanziamento / Financed by:

La copertura finanziaria graverà sui fondi/progetto:

- Risorse d'Ateneo: bando interno finanziamento assegni 2023 (D.R. n. 406/2023);
- Progetto/fondi: RICLIB_DAMANTE.

Requisiti di ammissione / Minimum qualifications necessary:

- Possesso del titolo di Dottore di ricerca o titolo equivalente conseguito all'estero;
- possesso di un curriculum scientifico professionale idoneo allo svolgimento dell'attività di ricerca contemplata.
- Research doctorate or equivalent qualification obtained abroad;
- professional scientific curriculum suitable for the research activity above mentioned.

Procedura selettiva / Competition procedure:

Valutazione per titoli e colloquio / Evaluation of titles and oral exam

I risultati della valutazione dei titoli saranno resi noti agli interessati nel corso del colloquio / The evaluation of the qualifications will be disclosed to candidates during the interview

Calendario del colloquio / Calendar of the oral exam	Modalità / Modality	In presenza / On site
	Data / Date	20 dicembre / December 2023
	Ora / Time	9:30 / 9:30 am (Italian time)
	Luogo / Place	Aula ex-presidenza presso il Dipartimento di area medica (DAME) Piazzale M. Kolbe, 4 – 33100 Udine (UD)

Per sostenere il colloquio i candidati devono esibire un valido documento di riconoscimento. / Candidates must come to the interview with a valid identity document.

Eventuali variazioni saranno rese note esclusivamente mediante pubblicazione all'albo ufficiale on line dell'Ateneo / Any change will be made public solely through publication on the University web site http://web.uniud.it/ateneo/normativa/albo_ufficiale

Commissione giudicatrice / Examining Board:

Nome e Cognome	**Qualifica**	**SSD**	**Università**
Membri Effettivi / Permanent members			
Giuseppe Damante	PO	MED/03	Università degli Studi di Udine
Carla Di Loreto	PO	MED/08	Università degli Studi di Udine
Gianluca Tell	PO	BIO/11	Università degli Studi di Udine
Membro Supplente / Temporary member			
Catia Mio	RTD	MED/03	Università degli Studi di Udine
Alessia Cimadamore	RTD	MED/08	Università degli Studi di Udine